Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3, 4, 6, 10-12, 19-24, and 26-36 are pending in the application, with claims 1, 23, 24, and 36 being the independent claims. Claims 2 and 25 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 3, 4, 23, 24, 26, 27, and 36 are sought to be amended. Support for the amendment of claims 1, 23, 24, and 36 may be found, *e.g.*, in original claim 2 and in the specification at, *e.g.*, page 2, lines 27-28. Claims 3, 4, 26, and 27 have been amended to maintain claim dependency. These changes are believed to introduce no new matter, and their entry is respectfully requested. Applicants reserve the right to prosecute the canceled subject matter in related applications.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated April 14, 2010, the Examiner has withdrawn the objection to claim 15 and the rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. The Examiner has maintained the rejections under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement and on the grounds of nonstatutory obviousness-type double patenting. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. Rejection of Claims 1, 3, 4, 6, 10-12, 19-21, 24, and 26-34 Under 35 U.S.C. § 112, First Paragraph, is Traversed

At pages 3-6 of the Office Action, the rejection of claims 1-4, 6, 10-12, and 19-21 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement has been maintained and has been applied to claims 24-34. The Examiner has reasserted that the specification is allegedly only enabling for "a method of promoting regeneration or survival of dopaminergic neurons in mammals injected with 6OHDA, by administering soluble NgR1 intracranially," but not for the full scope of the claims, including claimed variants. *See* Office Action, page 3. The Examiner's main argument in support of the rejection is that the 6-OHDA model described in Examples 1 and 2 of the specification, which was used in rats and in Nogo receptor knockout mice to demonstrate a link between Nogo receptor and dopaminergic neuronal degeneration, does not sufficiently enable the skilled artisan to practice the invention without undue experimentation. Applicants respectfully disagree. The Examiner's responsive arguments mischaracterize the claimed invention and misapply the law.

A. Summary of Claimed Subject Matter and Applicants' Invention

Applicants claim methods of promoting regeneration or survival of dopaminergic neurons in a mammal displaying signs or symptoms of dopaminergic neuronal degeneration. *See* claims 1 and 24. The methods comprise administering a therapeutically effective amount of a soluble form of a mammalian NgR1 or an antibody or antigen-binding fragment thereof that binds to a murine or human NgR1. Furthermore, in an effort to advance prosecution, and not in acquiescence to the

Examiner's rejection, Applicants have amended claims 1 and 24 such that the soluble form of a mammalian NgR1 or an antibody or antigen-binding fragment thereof that binds to a murine or human NgR1 is administered directly into the central nervous system.

The claimed methods are based on Applicants' discovery that blocking Nogo receptor protects dopaminergic neurons from degeneration caused by a dopaminergic neuron-specific neurotoxin, 6-OHDA. *See* specification, pages 16-18. Animal models using 6-OHDA to damage dopaminergic neurons are extensively characterized and have been used for the screening and preclinical testing of therapies to protect these neurons from degeneration. Using 6-OHDA models in rats and in Nogo receptor knockout mice, Applicants demonstrated a link between Nogo receptor and dopaminergic neurons. More significantly, Applicants showed that by using either a soluble NgR1 or the Nogo receptor gene knockout, the 6-OHDA treated rats and Nogo receptor knockout mice had increased dopaminergic neuronal survival and that soluble NgR1 increased levels of dopamine in the lesioned striatum. *See id.* at page 17, lines 7-14, and page 18, lines 4-10. Thus, Applicants demonstrated that knocking down Nogo receptor increased neuronal survival and improved recovery in dopaminergic pathways in the brain after injury.

B. Claims 1, 3, 4, 6, 10-12, 19-21, 24, and 26-34 are Enabled

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie*

case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). Applicants respectfully submit that the reasons for the rejection, as set forth in the Office Action, are insufficient to establish a *prima facie* case of non-enablement.

1. The Specification Enables Methods of Promoting Regeneration or Survival of Dopaminergic Neurons

The primary reason why the Examiner appears to doubt the "truth or accuracy" of the enablement of the claimed methods is that the 6-OHDA model used to identify the link between Nogo receptor and dopaminergic neuronal survival allegedly somehow fails to "mimic[] all or many neurodegenerative diseases that would fall into the genus" encompassed by the claims. Office Action, page 6. Yet, beyond the assertion itself, the Examiner provides no evidence in support thereof. Further, although the Examiner appears to acknowledge the validity of 6-OHDA as an experimental model "that focuses on destruction only of dopaminergic cells," the Examiner hastily concludes, *e.g.*, that the use of 6-OHDA in Nogo-receptor knockout mice cannot "provide evidence to support a method of treatment of human beings with neurodegenerative diseases."[1] *Id.* at pages 5-6. Applicants respectfully disagree with the Examiner's assertions.

[1] Applicants note that in the context of this statement, and throughout the Office Action, the Examiner frequently refers to "NOGO" and "NOGO-knockout mice." *See id.* at pages 5-6. Nogo is a ligand that binds to NgR1, and while the two molecules interact, the claimed methods and Examples do not

First, Applicants submit that mere breadth of a claim does not make a claim not enabled or indefinite as long as the scope of the subject matter that is embraced is clear. *In re Miller*, 441 F.2d 689 (CCPA 1971); MPEP 2173.04. Applicants respectfully point out that claims 1 and 24 are directed to methods of promoting regeneration or survival of dopaminergic neurons in a mammal displaying signs or symptoms of *dopaminergic neuronal degeneration*, not all dopaminergic brain disorders and not all neurodegenerative diseases as characterized by the Examiner. Thus, Applicants' claimed methods are applicable to those dopaminergic brain disorders that are characterized by the loss or degeneration of dopaminergic neurons. *See, e.g.*, specification, page 2, lines 6-14.

Next, Applicant's respectfully assert that the specification describes an established model of dopaminergic injury using 6-OHDA, which specifically destroys dopaminergic neurons. *See, e.g.*, specification, pages 16-18, Examples 1 and 2. Following the Applicants' Examples, one of ordinary skill could readily apply results from the 6-OHDA model to treat those dopaminergic brain disorders that are characterized by the loss or degeneration of dopaminergic neurons. In support of this argument, Applicants submit herewith under 37 C.F.R. § 1.132 the Declaration of Dr. Stephen M. Strittmatter ("the Strittmatter Declaration"). As explained therein, and in the cited literature references, the 6-OHDA model is well characterized and has been used extensively in various organisms to test whether a particular agent promotes regeneration or increases the survival of dopaminergic neurons. The 6-OHDA model is used in

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use Nogo ligand or Nogo ligand knockout mice. Rather, the claimed methods and Examples use a soluble form of mammalian NgR1, antibodies or antigen binding fragments that bind to a murine or human NgR1, or Nogo *receptor* knockout mice.

preclinical testing of therapies to improve the symptoms of diseases associated with dopaminergic neuronal degeneration such as Parkinson's disease.

Furthermore, Dr. Strittmatter explains that the 6-OHDA is a model in which a link has been well established between dopaminergic neuronal degeneration and pathologies related to diseases such as Parkinson's disease. Thus, based on the specificity of the 6-OHDA model, any data and findings would be applicable to all dopaminergic brain disorders that are characterized by the degeneration of dopaminergic neurons. For example, as described in the specification, Parkinson's disease is associated with progressive destruction of dopaminergic neurons in the substantia nigra. *See* specification, page 1, lines 10-11. Other diseases associated with degeneration of dopaminergic neurons include multiple system atrophy, striatonigral degeneration, olivopontocerebellar atrophy, Shy-Drager syndrome, motor neuron disease with parkinsonian features, Lewy body dementia, progressive supranuclear palsy, cortical-basal ganglionic degeneration, frontotemporal dementia, Alzheimer's disease with parkinsonism, Wilson disease, Hallervorden-Spatz disease, Chediak-Hagashi disease, SCA-3 spinocerebellar ataxia, X-linked dystonia-parkinsonism (DYT3), Huntington's disease (Westphal variant), prion disease, vascular parkinsonism, cerebral palsy, repeated head trauma, postencephalitic parkinsonism and neurosyphilis. *Id.* at page 2, lines 6-14.

Using 6-OHDA, which specifically injures dopaminergic neurons, Applicants found that blocking NgR1, either using a soluble NgR1 polypeptide or a mouse NgR1 knockout strain, increased survival of dopaminergic neurons in the substantia nigra and improved recovery in dopaminergic pathways. *See id.* at pages 16-18. Therefore, Applicants respectfully assert that it would require no more than routine experimentation

for any skilled artisan to practice the full scope of the claimed methods in view of the teachings in the specification and the knowledge available in the art regarding the use of 6-OHDA as a model for dopaminergic neuronal degeneration.

2. The Specification Enables Variants of a Soluble Form of a Mammalian NgR1

The Examiner maintains that the specification allegedly does not enable variants of NgR1, such as recited in claim 6, for use in the methods of the invention. *See* Office Action, page 6. While the Examiner agrees that the mutation of coding sequences to generate variants is routine, the Examiner contends that "[t]here is not enough experimental evidence that polypeptides with up to ten substitutions function **just like sNgR1**, such that the genus is enabled and the newly-made variants inhibit NOGO receptor-mediated activity with the same affinity and specificity as the one soluble receptor 'antagonist' described in the specification." *Id.* Applicants respectfully disagree with the Examiner's maintained position and assert that it simply does not reflect the state of law.

In re Wands, which is still good law, says that some experimentation, *e.g.*, testing and screening, even a considerable amount in order to make the invention, is not "undue" if, *e.g.*, it is merely routine. 858 F.2d 731, 737 (Fed. Cir. 1988). Furthermore, experimentation, even complex experimentation, is not undue if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). In the biological arts, screening for molecules that possess a particular activity is common. Thus, not only would it be routine to obtain, *e.g.*, a soluble form of a

mammalian NgR1 comprising amino acids 26 to 310 of human NgR1 (SEQ ID NO:3) with up to ten conservative amino acid substitutions, as acknowledged by the Examiner, but it would also be routine to (b) test them for the ability to promote regeneration or survival or dopaminergic neurons using, *e.g.*, the 6-OHDA model described in the specification.

Wands serves as a good example of the amount of screening that was common in the biological arts, even some *20* years ago when it was decided. For example, in concluding that practicing the claimed invention would not require undue experimentation, the court in *Wands* stated that, "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas [often hundreds at a time] to determine which ones secrete antibody with desired characteristics[, and p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Wands*, 858 F.2d at 738, 740, 8 USPQ2d at 1405, 1406. Much like the practitioners in *Wands* screening hundreds of hybridomas for monoclonal antibodies with the desired characteristics, one of skill in the art would be expected to engage in screening for polypeptides comprising amino acids 26 to 310 of human NgR1 (SEQ ID NO:3) with up to ten conservative amino acid substitutions and that promote regeneration or survival or dopaminergic neurons. Such screening, even if it resulted in the identification of a molecule not having the desired activity, would be considered routine in the art and would be acknowledged as an integral part of making the polypeptides.

As previously pointed out in Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed December 18, 2009, the skilled artisan could readily ascertain which

conservative amino acid substitutions to make in, *e.g.*, SEQ ID NO:3, in view of the specification and the knowledge available in the art. By simply comparing the human and rat NgR1 sequences provided in the specification at page 8, Table 2, one of skill in the art could identify any differences between these conserved sequences, which both bind Nogo ligand and share 87-89% sequence identity.[2] Furthermore, the Barton *et al.* reference identified by the Examiner in the Office Action of September 24, 2009, provides a detailed structural analysis of NgR1 in comparison to other NgR homologs and leucine-rich repeat-containing proteins, to which the skilled artisan could refer for determining what amino acid variations would be tolerated. *See, e.g.*, Barton *et al.*, page 3293, col. 1 to 3298, col. 1 and Figure 2.

Once obtained, the soluble NgR1 polypeptides with up to ten conservative amino acid substitutions could be tested in the 6-OHDA animal model provided in the Examples for the ability to promote regeneration or survival of dopaminergic neurons. Such testing, as discussed above, would be considered to be routine. Any inactive variants would be excluded because the claimed methods are directed to those soluble NgR1 polypeptides that promote regeneration or survival of dopaminergic neurons, not those variants that do not promote regeneration or survival of dopaminergic neurons.

Accordingly, Applicants submit that a person having ordinary skill in the art, in view of the teachings of the specification and the knowledge in the art, would be able to make and practice the full scope of Applicants' claimed methods. Moreover, Applicants contend that the Examiner has failed to provide acceptable objective evidence or sound

[2] Applicants note that a peptide with up to ten conservative amino acid substitutions of amino acids 26 to 310 of SEQ ID NO:3, for example, would have a percent identity of approximately 96% or greater when compared to amino acids 26 to 310 of SEQ ID NO:3 without substitutions.

scientific reasoning that shows that it would require undue experimentation for one of skill in the art to make and use the claimed invention, and therefore has failed to establish a *prima facie* case of non-enablement. Thus, Applicants respectfully request that this rejection be reconsidered and withdrawn.

IV. Rejection of Claims 22, 23, 35, and 36 Under 35 U.S.C. § 112, First Paragraph, is Traversed

At pages 6-8 of the Office Action, the rejection of claims 22 and 23 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement has been maintained and has been applied to claims 35 and 36. The Examiner has maintained the rejection allegedly because "[A]pplicants have failed to demonstrate a nexus between Parkinson's disease and NgR1, such that administration of sNgR1 will slow or reverse the loss of cells in the substantia nigra." *See* Office Action, page 7. The Examiner has also stated that "[t]here is no data showing that the soluble NgR1 receptor is effective in treating a patient with Parkinson's disease or even an animal model of Parkinson's disease." *Id.* Applicants respectfully disagree with these statements.

First, despite the Examiner's acknowledgement that clinical efficacy is not a requirement of enablement, the Examiner maintains to the contrary that "[t]here is no data showing that the soluble NgR1 receptor is effective in treating a patient with Parkinson's disease." *Id.* A requirement to show that soluble NgR1 is *effective in treating* a patient is not consonant with the state of the law. There is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. However, the Examiner still appears to suggest that for the claimed invention to be enabled, Applicants *must* demonstrate that the methods are without obstacles and therapeutically effective, *i.e.*, clinical efficacy. This is simply not the state of the law—

Applicants are not required to show clinical efficacy as a predicate to enabling the claimed invention.

Furthermore, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph).

As discussed above and in the Strittmatter Declaration, Examples 1 and 2 describe the use of 6-OHDA in an established animal model for screening anti-Parkinsonian agents. *See* specification, pages 16-18. Thus, the Examiner's statement that there is not even "an animal model of Parkinson's disease," is completely erroneous. Furthermore, under *Cross* and *Brana*, one of ordinary skill would recognize that the animal testing described in the present specification would be "generally predictive of *in vivo* test results," *Cross*, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed methods would be successful for the claimed *in vivo* therapeutic approaches.

In addition, Applicants respectfully disagree with the Examiner's statement directed to demonstrating "a nexus between Parkinson's disease and NgR1, such that administration of sNgR1 will *slow or reverse the loss of cells in the substantia nigra*." Office Action, page 7 (emphasis added). As discussed above and in the Strittmatter Declaration, the 6-OHDA model is used in preclinical testing of therapies to improve the symptoms of diseases associated with dopaminergic neuronal degeneration such as Parkinson's disease. Using 6-OHDA, which specifically injures dopaminergic neurons, Applicants found that blocking NgR1 with a soluble NgR1 polypeptide, increased survival of dopaminergic neurons in the substantia nigra and improved recovery in dopaminergic pathways. *See* specification, page 17, lines 7-14. Thus, in contrast to the Examiner's assertion, the specification demonstrates that administration of soluble NgR1 slows or reverse the loss of cells in the substantia nigra.

The Examiner has also alleged that the specification fails to teach one of skill in the art how to use sNgR1 to treat a subject, such as route of administration, duration, quantity, or "even a single working example of the sNgR1 ligand[3] being used to treat Parkinson's disease." Office Action, page 7. Applicants note that the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970). Nonetheless, Applicants' Examples provide one means of administering the soluble NgR1 polypeptides, *e.g.*, intracranially, in a method of promoting regeneration or survival of

[3] To avoid any confusion between the terminology for Nogo receptor and Nogo ligand, *see* note 1 *supra*, Applicants have interpreted this statement to refer to a soluble Nogo receptor, not a soluble Nogo ligand.

dopaminergic neurons. Moreover, the specification provides additional means well-known to those in the art for administering directly to the central nervous system[4] the specific NgR1 antagonists to a mammal displaying signs or symptoms of dopaminergic neuronal degeneration. *See, e.g.*, specification at page 11, line 13 to page 15, line 27. Applicants respectfully assert that the level of skill in the art is high. Thus, based on the clear guidance in the specification and knowledge in the art, one of ordinary skill, *e.g.* a neurobiologist or specialist physician, would easily be able to determine the amount needed to elicit a desired therapeutic effect in a subject in need of treatment without resorting to undue experimentation.

Therefore, Applicants submit that a person having ordinary skill in the art, in view of the teachings of the specification and the knowledge in the art, would be able to make and practice the full scope of Applicants' claimed invention. As described above, Applicants contend that the Examiner has failed to establish a *prima facie* case of non-enablement. Accordingly, Applicants respectfully request that the rejection of claims 22, 23, 35, and 36 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. Double Patenting Rejection is Traversed

At page 8 of the Office Action, the rejection of claims 22 and 23 under the judicially created doctrine of obviousness-type double patenting over claims 103 and 104 of U.S. Patent Appl. No. 12/335,328, has been maintained. Applicants respectfully traverse this rejection. However, Applicants request that this rejection continue to be held in abeyance until subject matter that is otherwise patentable is identified.

[4] Solely in an effort to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 23 and 36 such that the soluble form of a mammalian NgR1 or an antibody or antigen-binding fragment thereof that binds to a murine or human NgR1 is administered directly into the central nervous system.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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